REMARKS

Claims 1-3, 6, and 7 stand rejected as allegedly failing to comply with the enablement requirement. Applicant has amended claim 1 to recite the precise culture medium composition disclosed in the specification. Applicant respectfully requests reconsideration of the rejection in view of the amendment and following arguments.

35 U.S.C. § 112

Claims 1-3, 6 and 7 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. The Office Action alleges that the claims contain subject matter which was not described in such a way to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant traverses this rejection for the reasons indicated below.

While disagreeing with the Examiner, to expedite the prosecution, Applicant has amended claim 1 to recite the precise culture medium composition disclosed in the specification at page 12, line 32 to page 14, line 25. Applicant expressly reserves the right to pursue canceled subject matter in continuation applications.

Accordingly, the rejection is moot and should be withdrawn.

CONCLUSION

Applicant respectfully requests reconsideration of the rejection of claims 1-3, 6 and 7 and allowance of the case. Should additional fees be required in connection with this matter, please charge our Deposit Account No. 23-0785 the necessary amount.

Respectfully submitted,

WOOD, PHILLIPS, KATZ,
CLARK & MORTIMER

By_____
Mark Polyakov, Reg. No. 54,377

By_____
John S. Mortimer, Reg. No. 30,407

August 31, 2007

500 West Madison Street
Suite 3800
Chicago, IL 60661
(312) 876-1800

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posed; (*wahrnehmbar*) noticeable, perceptible; (*deutlich*) marked; (*offenbar, sichtlich*) obvious, evident, clear; ***ohne ~en Erfolg*** without any apparent (*od.* noticeable, appreciable) success; ***ohne ~en Grund*** for no apparent reason; **II.** *Adv.*: ***es/er hat sich ~ gebessert*** there's been / he's shown a noticeable (*od.* marked) improvement; **Sichtbarkeit** *f* visibility

Sicht|behinderung *f* poor visibility (***durch*** due to); **~beton** *m* exposed concrete; **~blende** *f* screen; **~einlage** *f Bank*: sight deposit

sichten *v/t.* **1.** (*sehen*) sight; **2.** (*durchsehen*) look (*od.* go) through; (*prüfend, sortierend*: sift through; (*ordnen*) sort (out)

Sicht|feld *n* field of view; **~fenster** *n* window; **~flug** *m Flug.* contact flight; **~grenze** *f* visibility limit; **~karte** *f* travel pass; (*Zeitkarte*) season ticket; **~kontakt** *m* eye contact

sichtlich **I.** *Adj.* visible; **II.** *Adv.* visibly; (*offensichtlich*) evidently

Sichtschutz *m* privacy fence (*od.* screen)

Sichtung *f* **1.** sighting; **2.** (*Überprüfung*) examination; (*Aussonderung*) sifting, sorting; ***nach ~ der Unterlagen*** after examining the documents

Sicht|verhältnisse *Pl.*: (***gute/schlechte***) **~** (good/poor) visibility *Sg.*; **~vermerk** *m* **1.** *im Pass*: visa; **2.** *Wirts.* endorsement; **~wechsel** *m Wirts.* bill payable on demand; **~weise** *f* view (of things); **~weite** *f* range of vision; ***in ~*** (with)in sight, within eyeshot; ***außer ~*** out of eyeshot

Sickergrube *f* soakaway, *Am.* dry well

sickern *v/i.* seep; (*tröpfeln*) trickle (***aus*** out of; ***in*** + *Akk.* into); (*auch* ***an die Öffentlichkeit***) **~** leak out; → *auch* ***durchsickern, einsickern***

Sickerwasser *n* **1.** *von Deich etc.*: seeping water, seepage; **2.** (rain)water seeping into the ground; (*Grundwasser*) groundwater

Sideboard ['saidbo:ɐd] *n*; *-s, -s* sideboard

Siderit *m*; *-s, -e*; *Min.* siderite

sie *pers. Pron.* **1.** *3. Person flSg.*: she, *Akk.* her; *Sache*: it; **2.** *3. Person Pl.*: they, *Akk.* them; **3.** ***Sie*** *Anrede*: you (*auch Akk.*); ***zu j-m Sie sagen*** → ***siezen***; ***wir sind immer noch per Sie*** we still call one another Sie; **Sie** *f*; *-, -s*; *umg.* **1.** ***es ist e-e ~*** *auch bei Tieren*: it's a she; **2.** *auf Badetüchern etc.*: hers

Sieb *n*; *-(e)s, -e* sieve; *für Flüssiges*: strainer; *für Gemüse*: colander; *für Sand etc.*: riddle, screen; *für Siebdruck*: screen; *für Öl, Benzin*: gauze filter; ***ein Gedächtnis wie ein ~*** *umg.* a memory like a sieve; **siebartig** *Adj.* sieve-like

Sieb|bein *n Anat.* ethmoid bone; **~druck** *m* silk-screen print (*Verfahren*: printing)

sieben[1] *vt/i.* (pass through a) sieve; (*Gemüse etc.*) *auch* strain, sift; (*Sand etc.*) riddle, screen; *fig.* sift through; ***da wird ganz schön gesiebt*** *fig.* they have a tough screening procedure, they really pick and choose *umg.*; → ***aussieben***

sieben[2] *Zahlw.* seven; → *auch* ***acht***[1]

Sieben *f*; *-, -en und - Zahl*: (number) seven; → ***Acht***[1] 1, 2, 4

sieben|armig *Adj.* seven-armed; **~er Leuchter** seven-branched candelabrum, *Reli.* menorah; **~bändig** *Adj. attr.* seven-volume ..., in seven volumes

Siebenbürgen (*n*); *-s*; *Geog.* Transylvania; **Siebenbürger** **I.** *m*; *-s, -*, **Siebenbürgerin** *f*; *-, -nen* Transylvanian (German), *weiblich auch*: Transylvanian (German) woman (*od.* girl); (*Aussiedler[in]*) *ethnic German from Transylvania*; **II.** *Adj.*: **~ Sachse** Transylvanian German; **siebenbürgisch** *Adj.* Transylvanian

Siebeneck *n* heptagon; **siebeneckig** *Adj.* heptagonal

Siebener *m*; *-s, -*; *umg.* (*Bus etc.*) number seven; → ***Sieben***

siebenfach *Adj.* sevenfold; **~e Menge** seven times the amount; **~er Sieger** seven-time winner (*od.* champion)

siebengescheit *Adj. umg.* smart-alecky

Siebengestirn *n Astron.*: ***das ~*** the Pleiades *Pl.*, the Seven Sisters *Pl.*

siebenhundert *Zahlw.* seven hundred

siebenjährig *Adj. attr.* **1.** seven-year-old ...; **2.** (*sieben Jahre dauernd*) seven-year ...; ***der Siebenjährige Krieg*** the Seven Years' War; **Siebenjährige** *m, f*; *-n, -n* seven-year-old

siebenköpfig *Adj. attr.* **1.** **~e Familie** *etc.* family *etc.* of seven; **2.** **~er Drache** seven-headed dragon

siebenmal *Adv.* seven times

Siebenmeilenstiefel *Pl. hum.* seven-league boots; ***mit ~n*** with giant strides

Siebenmeter *m Sport* penalty; **~linie** *f* penalty line

Siebenmonatskind *n Med.* seven-month baby

Sieben|pfünder *m*; *-s, -*; *umg.* seven-pound baby *etc.*; (*Fisch*) seven-pounder; **~sachen** *Pl. umg.* (all one's) things; **~schläfer** *m* **1.** *Zool.* (edible *od.* fat) dormouse; ***Gemeiner ~*** common dormouse; **2.** *nur Sg.*; 27th June (*the weather on this day being said to determine that of the next seven weeks*); *etwa* St (*od.* St.) Swithin's Day

sieben|seitig *Adj.* seven-sided, heptagonal; **~stellig** *Adj. attr. Zahl*: seven-figure ...; **~stöckig** *Adj. attr.* seven-stor(e)y ...; ***~ sein*** have seven storeys; **~stündig** *Adj. attr.* seven-hour(-long) ...

siebent *etc.* → ***siebt*** *etc.*; ***Siebenter Himmel*** *Islam*: seventh heaven; ***im ~en Himmel*** *umg. fig.* in seventh heaven, on cloud nine

siebentägig *Adj.* **1.** *attr.* seven-day (--long) ..., ... of a week; ***~ sein*** last seven days (*od.* a week); **2.** (*sieben Tage alt*) seven-day-old ..., week-old ...

siebentausend *Zahlw.* seven thousand; **Siebentausender** *m* seven-thousand met|re (*Am.* -er) (*etwa* twenty-three thousand foot) peak

siebenteilig *Adj. attr.* seven-part ...; *auch präd.* in seven parts

Sieb(en)tel *n*; *-s, -* seventh

sieb(en)tens *Adv.* seventh(ly), seven

Siebmaschine *f Tech.* screener, sifter

siebt *Adv.* seven of; ***sie waren zu ~*** there were seven of them; ***wir gingen zu ~ hin*** seven of us went

siebt... *Zahlw.* seventh; **~es Kapitel** chapter seven; ***am ~en März*** on the seventh of March, on March the seventh; ***7. März*** 7th March, March 7(th)

Siebte *m, f*; *-n, -n* (the) seventh; ***er war ~r*** he was (*od.* came) seventh; ***Eduard VII.*** Edward VII (= Edward the Seventh); ***an jedem ~n*** on every seventh day of the month

siebzehn *Zahlw.* seventeen; ***Siebzehn und Vier*** *Kartenspiel*: pontoon, *Am.* blackjack; **siebzehnt** *Zahlw.* seventeenth; **Siebzehntel** *n* seventeenth (part)

17-Zöller *m*; *-s, -*; (*Bildschirm*) 17-inch monitor

siebzig *Zahlw.* seventy; ***Anfang/Mitte/Ende ~ sein*** be in one's early/mid/late seventies; → *auch* ***achtzig***

Siebzig *f*; *-, -en, mst Sg. Zahl*: (number) seventy; → *auch* ***Achtzig***

siebziger *Adj.*: ***in den ~ Jahren*** in the seventies; ***sie ist in den Siebzigern*** she's in her seventies

Siebziger *m*; *-s, -*, **~in** *f*; *-, -nen* man/woman in his/her seventies; *förm.* septuagenarian; seventysomething *umg.*

Siebzigerjahre *Pl.*: ***in den ~n*** in the seventies

siebzigjährig *Adj. attr. Person*: seventy-year-old ...; *Zeitraum*: seventy-year ...

siebzigst... *Zahlw.* seventieth; ***sie hat heute ihren Siebzigsten*** she's seventy today, it's her seventieth birthday today

siech *Adj. altm. od. fig. geh.* infirm, ailing; *fig. Industrie etc.*: ailing; → ***dahinsiechend***; **Siechtum** *n*; *-s, kein Pl.*; *altm.* infirmity; *fig.* sickliness

siedeln *v/i.* settle; ***das Bienenvolk hat gesiedelt*** *fig.* the bees have colonized the hive

sieden; *siedete od. sott, hat gesiedet od. gesotten* **I.** *v/i.* (*siedete, hat gesiedet*) boil; (*simmern*) simmer; *fig. auch* seethe; ***es siedete in ihr*** she was seething (inside *od.* with rage, anger); **II.** *v/t.* (*mst sott, hat gesotten*) boil; *langsam*: simmer; ***Seife ~*** *altm.* obtain soap by boiling; → ***gesotten***, ***hart*** II 1; **siedend** **I.** *Part. Präs.* → ***sieden***; **II.** *Adj.* boiling; *fig. auch* seething; ***in ~er Hitze*** in sweltering heat; **III.** *Adv.*: ***~ heiß*** scalding (hot), boiling (*Essen*: piping) hot; ***da fiel mir ~ heiß ein*** *umg.* it suddenly struck me with horrible clarity, I suddenly remembered to my horror (*od.* with a shock)

Siede|punkt *m* boiling point (*auch fig.*); *fig. Pol. auch* flashpoint; ***den ~ erreichen*** *fig.* reach boiling point (*od.* a flashpoint); **~wasserreaktor** *m* boiling water reactor

Siedler *m*; *-s, -*, **~in** *f*; *-, -nen* settler

Siedlung *f* **1.** settlement; **2.** ([*Neu*]*Baugebiet*) (housing) development (*Brit. auch* estate)

Siedlungs|dichte *f* population density; **~form** *f* type of settlement; **~gebiet** *n* settlement (area); **~geschichte** *f* settlement history; **~gesellschaft** *f* housing association (*buying land for development*); **~haus** *n* house on a development, *Brit. auch* estate house; **~land** *n* land for development; **~politik** *f* settlement policies *Pl.*; **~raum** *m* settlement area; **~stopp** *m* cessation of development

Sieg *m*; *-es, -e* victory; *Sport etc.*: *auch* win; *fig. des Guten etc.*: triumph; ***leichter ~*** easy victory (*od.* win); ***den ~ davontragen*** be victorious, carry (*od.* win) the day *lit.*; ***knapp den ~ verfehlen*** be narrowly beaten; ***auf ~ spielen*** *Sport* play to win (*od.* for a win); ***der Vernunft etc. zum ~ verhelfen*** help common sense *etc.* to gain the upper hand; **~chance** *f* chance of victory (*od.* of winning)

Siegel *n*; *-s, -* seal (*auch fig.*); ***ein ~ anbringen/aufbrechen*** fix/break a seal; ***ein Buch mit sieben ~n*** *fig.* a closed book (+ *Dat. od.* ***für*** to); ***er hat es mir***

S

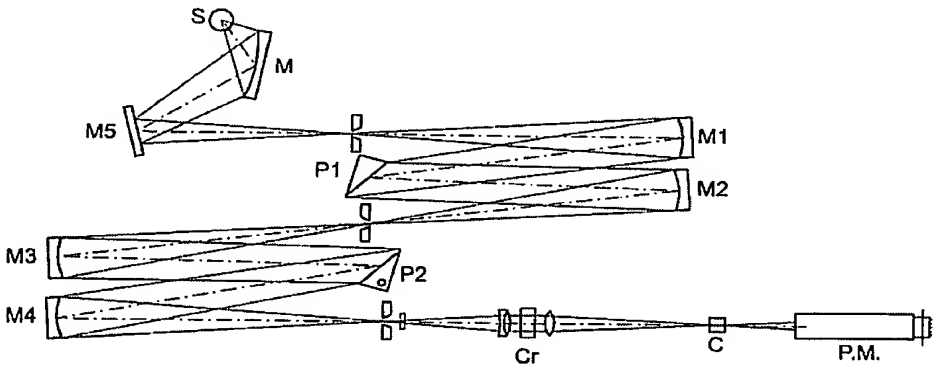

Figure 2.2.41.-1. – *Optical scheme of a dichrograph*

M = relative molecular mass of the substance to be examined,

c = concentration of the solution to be examined in g/ml,

l = optical path of the cell in centimetres.

Molar ellipticity is also related to molar circular dichroism by the following equation:

$$[\Theta] = 2.303\Delta\varepsilon\frac{4500}{\pi} \approx 3300\Delta\varepsilon$$

Molar ellipticity is often used in the analysis of proteins and nucleic acids. In this case, molar concentration is expressed in terms of monomeric residue, calculated using the expression:

$$\frac{\text{molecular mass}}{\text{number of amino acids}}$$

The mean relative molecular mass of the monomeric residue is 100 to 120 (generally 115) for proteins and about 330 for nucleic acids (as the sodium salt).

Apparatus. The light source (S) is a xenon lamp (Figure 2.2.41.-1); the light passes through a double monochromator (M) equipped with quartz prisms (P1, P2).

The linear beam from the first monochromator is split into 2 components polarised at right angles in the second monochromator. The exit slit of the monochromator eliminates the extraordinary beam.

The polarised and monochromatic light passes through a birefringent modulator (Cr): the result is alternating circularly polarised light.

The beam then passes through the sample to be examined (C) and reaches a photomultiplier (PM) followed by an amplifier circuit which produces 2 electrical signals: one is a direct current V_c and the other is an alternating current at the modulation frequency V_{ac} characteristic of the sample to be examined. The phase gives the sign of the circular dichroism. The ratio V_{ac}/V_c is proportional to the differential absorption ΔA which created the signal. The region of wavelengths normally covered by a dichrograph is 170 nm to 800 nm.

Calibration of the apparatus

Accuracy of absorbance scale. Dissolve 10.0 mg of *isoandrosterone R* in *dioxan R* and dilute to 10.0 ml with the same solvent. Record the circular dichroism spectrum of the solution between 280 nm and 360 nm. Measured at the maximum at 304 nm, $\Delta\varepsilon$ is + 3.3.

The solution of *(1S)-(+)-10-camphorsulphonic acid R* may also be used.

Linearity of modulation. Dissolve 10.0 mg of *(1S)-(+)-10-camphorsulphonic acid R* in *water R* and dilute to 10.0 ml with the same solvent. Determine the exact concentration of camphorsulphonic acid in the solution by ultraviolet spectrophotometry (*2.2.25*), taking the specific absorbance to be 1.49 at 285 nm.

Record the circular dichroism spectrum between 185 nm and 340 nm. Measured at the maximum at 290.5 nm, $\Delta\varepsilon$ is + 2.2 to + 2.5. Measured at the maximum at 192.5 nm, $\Delta\varepsilon$ is −4.3 to −5.

(1S)-(+)- or antipodal *(1R)-(−)-ammonium 10-camphorsulphonate R* can also be used.

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2.2.42. DENSITY OF SOLIDS

The density of solids corresponds to their average mass per unit volume and typically is expressed in grams per cubic centimetre (g/cm³) although the International Unit is the kilogram per cubic meter (1 g/cm³ = 1000 kg/m³).

Unlike gases and liquids whose density depends only on temperature and pressure, the density of a solid particle also depends on its molecular assembly and therefore varies with the crystal structure and degree of crystallinity.

When a solid particle is amorphous or partially amorphous, its density may further depend upon the history of preparation and treatment.

Therefore, unlike fluids, the densities of two chemically equivalent solids may be different, and this difference reflects a difference in solid-state structure. The density of constituent particles is an important physical characteristic of pharmaceutical powders.

The density of a solid particle can assume different values depending on the method used to measure the volume of the particle. It is useful to distinguish three levels of expression of density:

- the *crystal density* which only includes the solid fraction of the material; the crystal density is also called *true density*;
- the *particle density* which also includes the volume due to intraparticulate pores,
- the *bulk density* which further includes the interparticulate void volume formed in the powder bed; the bulk density is also called *apparent density*.

CRYSTAL DENSITY

The crystal density of a substance is the average mass per unit volume, exclusive of all voids that are not a fundamental part of the molecular packing arrangement. It is an intrinsic property of the substance, and hence should

be independent of the method of determination. The crystal density can be determined either by calculation or by simple measurement.

A. The *calculated crystal density* is obtained using crystallographic data (size and composition of the unit cell) of a perfect crystal, from for example X-ray diffraction data, and the molecular mass of the substance.

B. The *measured crystal density* is the mass to volume ratio after measuring the monocrystal mass and volume.

PARTICLE DENSITY

The particle density takes into account both the crystal density and the intraparticulate porosity (sealed and/or open pores). Thus, particle density depends on the value of the volume determined which in turn depends on the method of measurement. The particle density can be determined using one of the two following methods.

A. The *pycnometric density* is determined by measuring the volume occupied by a known mass of powder which is equivalent to the volume of gas displaced by the powder using a gas displacement pycnometer (*2.9.23*). In pycnometric density measurements, the volume determined includes the volume occupied by open pores; however, it excludes the volume occupied by sealed pores or pores inaccessible to the gas. Due to the high diffusivity of helium, which is the preferred choice of gas, most open pores are accessible to the gas. Therefore, the pycnometric density of a finely milled powder is generally not very different from the crystal density.

B. The *mercury porosimeter density* is also called *granular density*. With this method the volume determined also excludes contributions from sealed pores; however, it includes the volume only from open pores larger than some size limit. This pore size limit or minimal access diameter depends on the maximal mercury intrusion pressure applied during the measurement and under normal operating pressures the mercury does not penetrate the finest pores accessible to helium. Various granular densities can be obtained from one sample since, for each applied mercury intrusion pressure, a density can be determined that corresponds to the pore size limit at that pressure.

BULK AND TAPPED DENSITY

The bulk density of a powder includes the contribution of interparticulate void volume. Hence, the bulk density depends on both the density of powder particles and the space arrangement of particles in the powder bed.

The bulk density of a powder is often very difficult to measure since the slightest disturbance of the bed may result in a new density. Thus, it is essential in reporting bulk density to specify how the determination was made.

A. The *bulk density* is determined by measuring the volume of a known mass of powder, that has been passed through a screen, into a graduated cylinder (*2.9.15*).

B. The *tapped density* is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken until little further volume change is observed (*2.9.15*).

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2.2.43. MASS SPECTROMETRY

Mass spectrometry is based on the direct measurement of the ratio of the mass to the number of positive or negative elementary charges of ions (*m/z*) in the gas phase obtained from the substance to be analysed. This ratio is expressed in atomic mass units (1 a.m.u. = one twelfth the mass of ^{12}C) or in daltons (1 Da = the mass of the hydrogen atom).

The ions, produced in the ion *source* of the apparatus, are accelerated and then separated by the *analyser* before reaching the *detector*. All of these operations take place in a chamber where a pumping system maintains a vacuum of 10^{-3} to 10^{-6} Pa.

The resulting spectrum shows the relative abundance of the various ionic species present as a function of *m/z*. The signal corresponding to an ion will be represented by several peaks corresponding to the statistical distribution of the various isotopes of that ion. This pattern is called the *isotopic profile* and (at least for small molecules) the peak representing the most abundant isotopes for each atom is called the *monoisotopic peak*.

Information obtained in mass spectrometry is essentially qualitative (determination of the molecular mass, information on the structure from the fragments observed) or quantitative (using internal or external standards) with limits of detection ranging from the picomole to the femtomole.

INTRODUCTION OF THE SAMPLE

The very first step of an analysis is the introduction of the sample into the apparatus without overly disturbing the vacuum. In a common method, called *direct liquid introduction*, the sample is placed on the end of a cylindrical rod (in a quartz crucible, on a filament or on a metal surface). This rod is introduced into the spectrometer after passing through a vacuum lock where a primary intermediate vacuum is maintained between atmospheric pressure and the secondary vacuum of the apparatus.

Other introduction systems allow the components of a mixture to be analysed as they are separated by an appropriate apparatus connected to the mass spectrometer.

Gas chromatography/mass spectrometry. The use of suitable columns (capillary or semi-capillary) allows the end of the column to be introduced directly into the source of the apparatus without using a separator.

Liquid chromatography/mass spectrometry. This combination is particularly useful for the analysis of polar compounds, which are insufficiently volatile or too heat-labile to be analysed by gas chromatography coupled with mass spectrometry. This method is complicated by the difficulty of obtaining ions in the gas phase from a liquid phase, which requires very special interfaces such as:

- *direct liquid introduction*: the mobile phase is nebulised, and the solvent is evaporated in front of the ion source of the apparatus,
- *particle-beam interface*: the mobile phase, which may flow at a rate of up to 0.6 ml/min, is nebulised in a desolvation chamber such that only the analytes, in neutral form, reach the ion source of the apparatus; this technique is used for compounds of relatively low polarity with molecular masses of less than 1000 Da,
- *moving-belt interface*: the mobile phase, which may flow at a rate of up to 1 ml/min, is applied to the surface of a moving belt; after the solvent evaporates, the components to be analysed are successively carried to the ion source of the apparatus where they are ionised; this technique is rather poorly suited to very polar or heat-labile compounds.

Other types of coupling (electrospray, thermospray, atmospheric-pressure chemical ionisation) are considered to be ionisation techniques in their own right and are described in the section on modes of ionisation.

Attach the permeability cell to the tube of the manometer by means of an airtight connection. Evacuate the air from the manometer by means of a rubber bulb until the level of the coloured liquid is at the highest mark. Close the tap and check that the apparatus is airtight by closing the upper end of the cell, for example with a rubber stopper. Remove the stopper and, using a timer, measure the time taken for the liquid to fall from the second to the third mark.

Using the measured flow time, calculate the specific surface area (S), expressed in square metres per gram, from the following expression:

$$S = \frac{K \times \sqrt{\varepsilon^3} \times \sqrt{t}}{\rho \times (1 - \varepsilon) \times \sqrt{\eta}} \qquad (2)$$

t = flow time in seconds,

η = dynamic viscosity of air in millipascal seconds (see Table 2.9.14.-1),

K = apparatus constant determined according to Equation (4),

ρ = density of the substance to be examined in grams per millilitre,

ε = porosity of the compacted bed of powder.

CALIBRATION OF THE APPARATUS

The bulk volume of the compacted bed of powder is determined by the mercury displacement method as follows:

Place two filter paper disks in the permeability cell, pressing down the edges with a rod slightly smaller than the cell diameter until the filter disks lie flat on the perforated metal disk; fill the cell with mercury, removing any air bubbles adhering to the wall of the cell and wipe away the excess to create a plane surface of mercury at the top of the cell. If the cell is made of material that will amalgamate, grease the cell and the metal disk first with a thin layer of liquid paraffin. Pour out the mercury into a tared beaker and determine the mass (M_A) and the temperature of the mercury.

Make a compacted bed using the reference powder and again fill the cell with mercury with a planar surface at the top of the cell. Pour out the mercury in a tared beaker and again determine the mass of the mercury (M_B). Calculate the bulk volume (V) of the compacted bed of powder from the following expression:

$$V = \frac{M_A - M_B}{\rho_{Hg}} \qquad (3)$$

$M_A - M_B$ = difference between the determined masses of mercury in grams,

ρ_{Hg} = density of mercury at the determined temperature in grams per millilitre.

Repeat the procedure twice, changing the powder each time; the range of values for the calculated volume (V) is not greater than 0.01 ml. Use the mean value of the three determined volumes for the calculations.

The apparatus constant K is determined using a reference powder with known specific surface area and density as follows:

Calculate the required quantity of the reference powder to be used (Eq. 1) using the stated density and the determined volume of the compacted powder bed (Eq. 3).

Homogenise and loosen up the powder by shaking it for 2 min in a 100 ml bottle. Prepare a compacted powder bed and measure the flow time of air as previously described. Calculate the apparatus constant (K) from the following expression:

$$K = \frac{S_{sp} \times \rho \times (1 - \varepsilon) \times \sqrt{\eta}}{\sqrt{\varepsilon^3} \times \sqrt{t}} \qquad (4)$$

S_{sp} = stated specific surface area of the reference powder,

ρ = density of the substance to be examined in grams per millilitre,

ε = porosity of the compacted bed of powder,

t = flow time in seconds,

η = dynamic viscosity of air in millipascal seconds (see Table 2.9.14.-1).

The density of mercury and the viscosity of air over a range of temperatures are shown in Table 2.9.14.-1.

Table 2.9.14.-1.

Temperature (°C)	Density of mercury (g/ml)	Viscosity of air (η) (mPa·s)	$\sqrt{\eta}$
16	13.56	0.01800	0.1342
17	13.56	0.01805	0.1344
18	13.55	0.01810	0.1345
19	13.55	0.01815	0.1347
20	13.55	0.01819	0.1349
21	13.54	0.01824	0.1351
22	13.54	0.01829	0.1353
23	13.54	0.01834	0.1354
24	13.54	0.01839	0.1356

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2.9.15. APPARENT VOLUME

The test for apparent volume is intended to determine under defined conditions the apparent volumes, before and after settling, the ability to settle and the apparent densities of divided solids (for example, powders, granules).

APPARATUS

The apparatus (see Figure 2.9.15.-1) consists of the following:

- a settling apparatus capable of producing in 1 min 250 ± 15 taps from a height of 3 ± 0.2 mm. The support for the graduated cylinder, with its holder, has a mass of 450 ± 5 g;
- a 250 ml graduated cylinder (2 ml intervals) with a mass of 220 ± 40 g.

METHOD

Into the dry cylinder, introduce without compacting 100.0 g (m g) of the substance to be examined. If this is not possible, select a test sample with an apparent volume between 50 ml and 250 ml and specify the mass in the expression of results. Secure the cylinder in its holder. Read the unsettled apparent volume V_0 to the nearest millilitre. Carry out 10, 500 and 1250 taps and read the corresponding volumes V_{10}, V_{500} and V_{1250}, to the nearest millilitre. If the difference between V_{500} and V_{1250} is greater than 2 ml, carry out another 1250 taps.

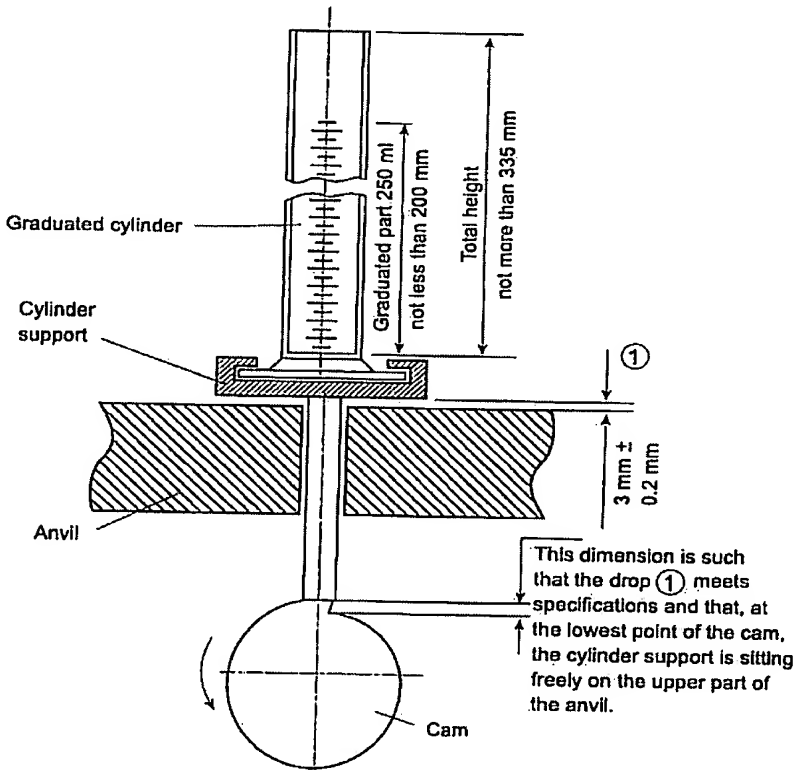

Figure 2.9.15.-1

EXPRESSION OF THE RESULTS

a) Apparent volumes:

- apparent volume before settling or bulk volume: V_0 ml.
- apparent volume after settling or settled volume: V_{1250} ml or V_{2500} ml.

b) Ability to settle: difference V_{10} ml − V_{500} ml.

c) Apparent densities:

The apparent densities are expressed as follows:

- apparent density before settling or density of bulk product: m/V_0 (grams per millilitre) (poured density).
- apparent density after settling or density of settled product: m/V_{1250} or m/V_{2500} (grams per millilitre) (tapped density).

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2.9.16. FLOWABILITY

The test for flowability is intended to determine the ability of divided solids (for example, powders and granules) to flow vertically under defined conditions.

APPARATUS

According to the flow properties of the material to be tested, funnels with or without stem, with different angles and orifice diameters are used. Typical apparatuses are shown in Figures 2.9.16.-1 and 2.9.16.-2. The funnel is maintained upright by a suitable device. The assembly must be protected from vibrations.

METHOD

Into a dry funnel, whose bottom opening has been blocked by suitable means, introduce without compacting a test sample weighed with 0.5 per cent accuracy. The amount of the sample depends on the apparent volume and the apparatus used. Unblock the bottom opening of the funnel and measure the time needed for the entire sample to flow out of the funnel. Carry out three determinations.

EXPRESSION OF RESULTS

The flowability is expressed in seconds and tenths of seconds, related to 100 g of sample.

The results depend on the storage conditions of the material to be tested.

The results can be expressed as the following:

a) the mean of the determinations, if none of the individual values deviates from the mean value by more than 10 per cent;

b) as a range, if the individual values deviate from the mean value by more than 10 per cent;

c) as a plot of the mass against the flow time;

d) as an infinite time, if the entire sample fails to flow through.